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Biomat _dBase: A Database on Biomaterials[#]

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Abstract: Biomaterial science provides a platform for the development of bio-artificial implants. Growth or development of engineered tissues for the purpose of repairing, restoring and enhancing the function of a damaged tissue or organ needs designed biomaterials. The most studied tissue engineering strategy consists on using cells growth factors and temporary three-dimensional (3D) porous scaffolds. 3D scaffolds play a very important role in the success of tissue engineering and regenerative medicine. They provide structural support for cells to proliferate and maintain their differentiated phenotype and permit the convenient delivery of cells into the patients. Several features of scaffold can influence the cell growth and its functions. The artificial extracellular matrices can be produced from different biomaterials including ceramics, natural or synthetic polymers and composites. Recent discoveries and innovations in this emerging field adopt varieties of techniques ranging from biotechnology to material science and nanotechnology. The result is a huge amount of data. To maintain and keep updated, this would not be an easy task. New advances in computers and information technology help to create and organize the databases quite easy. Their contents can easily be accessed, managed and updated. A WWW interface benefits the users to search the different types of data based on the types of biomaterials, their abundance, structure and applications. This provides the scope and archive of information on this emerging field of biomaterials to the global scientific community. The database is freely accessible through http://dbbiomat.iitkgp.ernet.in.

Keywords: Biomaterials, BLAST, database, relational database, tissue engineering.

INTRODUCTION

Traditionally, biomaterials are intended to treat, deliver, augment or replace either the tissue or the function of body damaged either by disease or trauma [1-5]. Recently natural or synthetic nonviable biomaterials should not only promote an appropriate host response to the body, but also promote or inhibit specific cell activities. In the last few decades, with the combined advancement of biomaterials and biological sciences, the new field of "tissue engineering" and "regenerative medicine" has emerged creating unique opportunities to fabricate tissues in the laboratory. Biomaterials play a pivotal role in this field of science that is being used for producing new skin, connective tissues like bone and cartilage [6-9]. Strategies to provide smart capabilities to the biomaterials primarily seek to achieve matrices that are instructive/inductive to cells. They may help to stimulate/trigger target cell responses, which are crucial in the tissue regeneration processes [10]. The development of such a tissue engineered construct required the combination of engineered extracellular matrices ("scaffolds"), cells and biologically active molecules. Cells are the fundamental unit on this strategy because of their ability to proliferate differentiate, and deposit specific ECM [11, 12]. Biomaterials used in tissue engineering applications can be fabricated in different forms including films, scaffold, nanofibers, nanoparticles, and hydrogels. Films basically have a 2D architecture and are able to support the adhesion and proliferation of cells [13]. Scaffolds are considered as a microporous three dimensional structures, in which a cell suspension can be seeded, promoting proliferation, differentiation, migration and orientation of the cells [7 and 14-17]. The nanofibers are sub-microscopic range fibers, dimensionally similar to ECM, which provide the cues for cell survival, their organization and function [18-21].[1]On the other hand nanoparticles are sub-microscopic size particles applied for the delivery of drug, vaccines, plasmid DNA, and other bioactive molecules [22-27]. Hydrogels are 3D structures involving a network of structural, usually cross-linked molecules, within a water-based viscous matrix

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[1] #Available at: http://dbbiomat.iitkgp.ernet.in
Log in: database
Password: biomat321

1875-0435/12

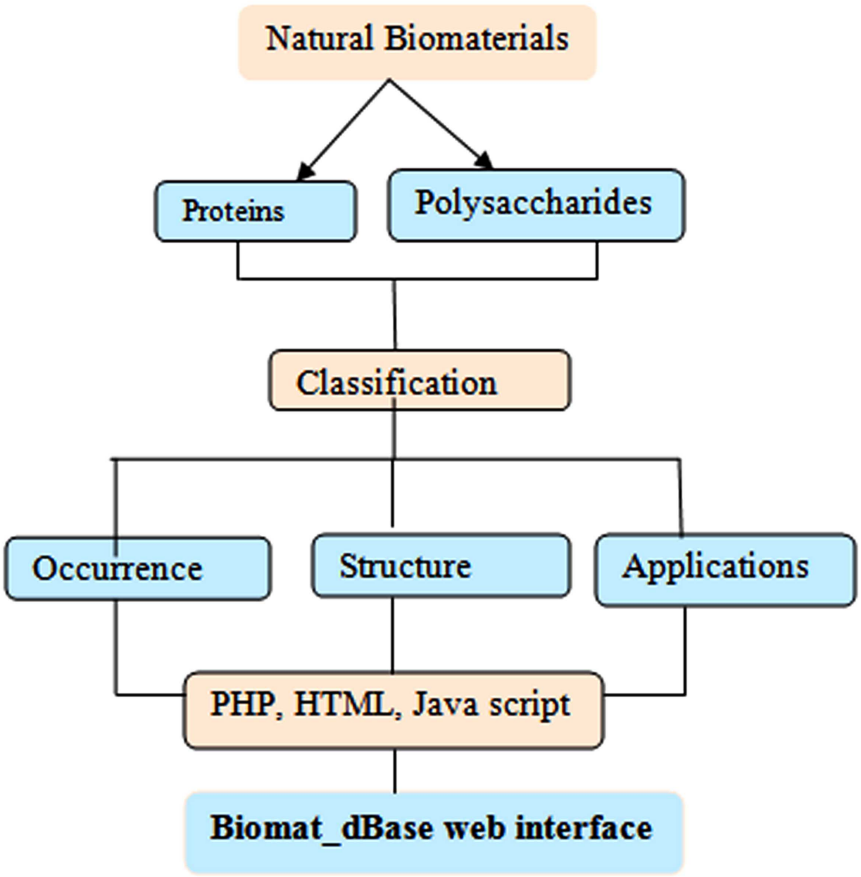

Fig. (1). Schematic diagram of Biomat_dBase web interface.

employed for cell encapsulation, delivery of drugs and other molecule [28-32]. Different types of natural and synthetic biomaterials are utilized for the fabrication of the polymeric matrices including starch, collagen, gelatin, alginate, agrose, chitosan, hyaluronic acid, silk proteins, elastin and fibrin [33-35]. One promising feature of these polymers is their excellent ability to be processed into porous structures use for the cell transplantation and tissue regeneration. Moreover, these natural biopolymers show similarity to the ECM and other polymers of the body [12]. ECM is complex mixture of structural and functional proteins, glycoprotein and proteoglycans arranged in a unique tissue specific three-dimensional ultra structure, that provide mechanical stability and structural integrity to tissues and organs [34]. Natural based biomaterials are widely used for tissue engineering applications due to their excellent biodegradability, antimicrobial property [35], biocompatibility, oxygen permeability and nontoxic nature. Examples of their use includes applications for wound dressing [36-38], tissue engineering of bone [39, 40], cartilage [41, 42], ligament [43, 44], skin [45], tendon [43, 46], hepatic [47], reticular connective tissue [48] endothelial and blood vessels [49, 50]. Other example includes its use for vaccine design [51] and for the detection of brain activity [52]. Despite progress, currently there are a few tissue-engineering products available for clinical use especially synthetic ones. They can substitute soft and mechanically functional tissues such as muscle and connective tissue [53].

A large number of discoveries and innovations have occurred in this field and thus a huge amount of data has been created. The management and updating of such a huge data is not an easy task. Thus, development of an appropriate biomaterial database is the need of the hour, which would allow the scientific community to be benefitted by the information given about the recent developments, prevents wasteful duplication of research and increase the faculty of knowledge for taking appropriate decision before initiation of new research. Based on these criteria, we have developed a database on biomaterials. It is available at http://dbbiomat.iitkgp.ernet.in. This derived database mainly focuses on the natural based biomaterials (protein and polysaccharides), site of occurrence of the biomaterials, structures and their applications.

MATERIALS AND METHODS

Biomaterial database is created using relational database management system (RDBMS) [54, 55] and operated in Red Hat Enterprise Linux 4. The web interface is developed in HTML/CSS; PHP and Java scripts are used for retrieving the stored data. The Basic Local Alignment Search Tools (BLAST) explore web interface and its scripts are implemented in PHP, based on [56-58]. The overall structure of the biomaterial database is shown in Fig. (**1**). The protein sequence corresponds to the biomaterials data collected from the protein data bank at www.rcsb.org/pdb. All the sequences are downloaded in a FASTA format and saved in a common database flat file. Then the database file is converted into a format acceptable by BLAST, using the Formatdb program [59]. The stand-alone version of the BLAST program is downloaded from the NCBI/BLAST web site (ftp://ftp.ncbi.nlm.nih.gov/blast/executables/release/LA-TEST/). To begin the search, an input parameter called

threshold has to be defined by the user. In the Biomat_dBase server, the input for the BLAST is provided in the text box in standard FASTA format. The input may also be uploaded from the client's local machine. The server takes the query from the input page and searches for similar homology sequences against the biomaterial database by using the BLASTP program. Finally, the similar protein sequences, which are obtained under the given threshold value is displayed in the new window. Data redundancy can be checked by the use of secondary structure matching tool (EBI-SSM) and Root Mean Squire Deviation (RMSD) to prevent the unnecessary duplication and redundancy in the database. The pictures of silk biomaterials are created on the webpage by using cascade style sheet (CSS) and java script.

DATABASE ACCESS AND INTERFACE

Biomaterial database is developed using relational database management system (RDBMS) and interfaced through the custom designed web interface by utilising Hypertext pre-processor (PHP), Hypertext Mark-up language (HTML) and JavaScript. The database is housed in a Sun Fire v880 Server running Solaris 9 (Sun Microsystems). The BLAST search, available in the Biomaterial database utilizes the formatted sequence data available in the relational database. The biomaterial database is freely available at a web based user interface site (http://dbbiomat.iitkgp.er-net.in). It allows users to explore the website and fetch the data corresponding to their queries. It also provides the information related to biomaterials, their sequence homology, percent sequence identity, information about the protein and polysaccharide biomaterials, their occurrences, structures and applications.

The structural component of biomaterial is solved using bioinformatics tools. The PDB ID of the related biomaterials is obtained from the protein data bank (PDB) [60] from http://www.rcsb.org/pdb. On the basis of their structure they are classified and stored in the RDBMS. It provides the following information about the description of a particular biomaterial:

a) How its structure is solved experimentally (X-RAY crystallography, NMR spectroscopy or Fiber diffraction method),

b) Resolution of the structure

c) Group of the protein or polysaccharide biomaterials (hydrolyses or celluloses etc),

d) Assembly type (whether DNA or RNA bound, protein chain and number of residues),

e) Nucleotide chain and number of residues, and

f) References of the structure.

RESULTS AND DISCUSSION

The main objective of this work is to construct a database for biomaterials. Currently there is no such database on this emerging field. In order to develop this, we use a relational database system. For example, we consider the basic local alignment and search tool (BLAST) for protein and polysaccharide database, to store the sequence in the sequence database and to implement the BLAST algorithms within the database system for the retrieval and analysis of sequence information [61]. BLAST is the most widely used algorithm for comparing biological sequences such as amino acids or nucleotides [62]. The query sequence is compared against a large database or library at a very high speed and produces the statistical significance of matching sequences. In addition, the program finds the regions of local similarity during the sequence alignment. Several variants of the BLAST program exist, of which the protein-protein BLAST (BLASTp) program is used for identifying a query of amino acid sequence and for finding similar sequences in protein databases. Thus, the BLAST can be used to infer functional and evolutionary relationships between sequences. In general, the BLAST output tends to be large and need to be processed to gain meaningful information. Several programs are developed to aid this process, which include the MuSeqBox [63], BioParser [64], the Nuclear BLAST program [65] and the PLAN web server [66]. All these programs aid in data mining of the BLAST results to generate more comprehensive outputs as required by the users.

PDB ID for protein and polysaccharide biomaterials is obtained from the Protein Data Bank. While creating a database, data redundancy becomes the biggest problem, where same data value is stored more than once in a table. This increases the size of data base unnecessarily, and leads to multiple display of search results leading to confusion and clutter in the database. Database redundancy can be checked by the use of secondary structure matching tool (EBI-SSM) for pair wise comparison and 3D alignment of the structures. Sequences that have higher sequence identity and best Root-mean-square deviation (RMSD) values are chosen. Those having lowest sequence identity and worst RMSD values are discarded. When multiple entry of a given structure is available in the PDB, we retain the one with the best resolution value. Between wild type and mutant proteins or polysaccharides, we kept the wild types to reduce the redundancy in the database.

The homepage of the database has modules for different matrices, classifications, search and references related to biomaterials. The home page module provides information related to the concept of biomaterials, their design criteria and classifications. A typical homepage module is presented in Fig. (**2A**). Modules for the matrices provide information on different types of fabricated biomaterial structures in the form of scaffolds, nanofibers, nanoparticles, hydrogels and films used for potential applications of different tissue engineering and regenerative medicine. Classification modules segregate the biomaterials into those of natural and synthetic origin are in Fig. (**2B**) and (**2C**) respectively. The natural biomaterials are further classified into proteins and polysaccharides on the basis of their occurrence, structure and applications. We have provided the detail list for synthetic biomaterials and their applications in a tabular form on the web page.

The search tool option has a drop down list box on biomaterials including silk, starch, agarose, alginate, carrageenans, cellulose, chitosan, collagen, elastin, fibrin, gelatin, hyaluronic acid, arabinogallactane, and glycosaminoglycan. They are structurally classified on the basis of their PDB ID, sequence of the related biomaterials

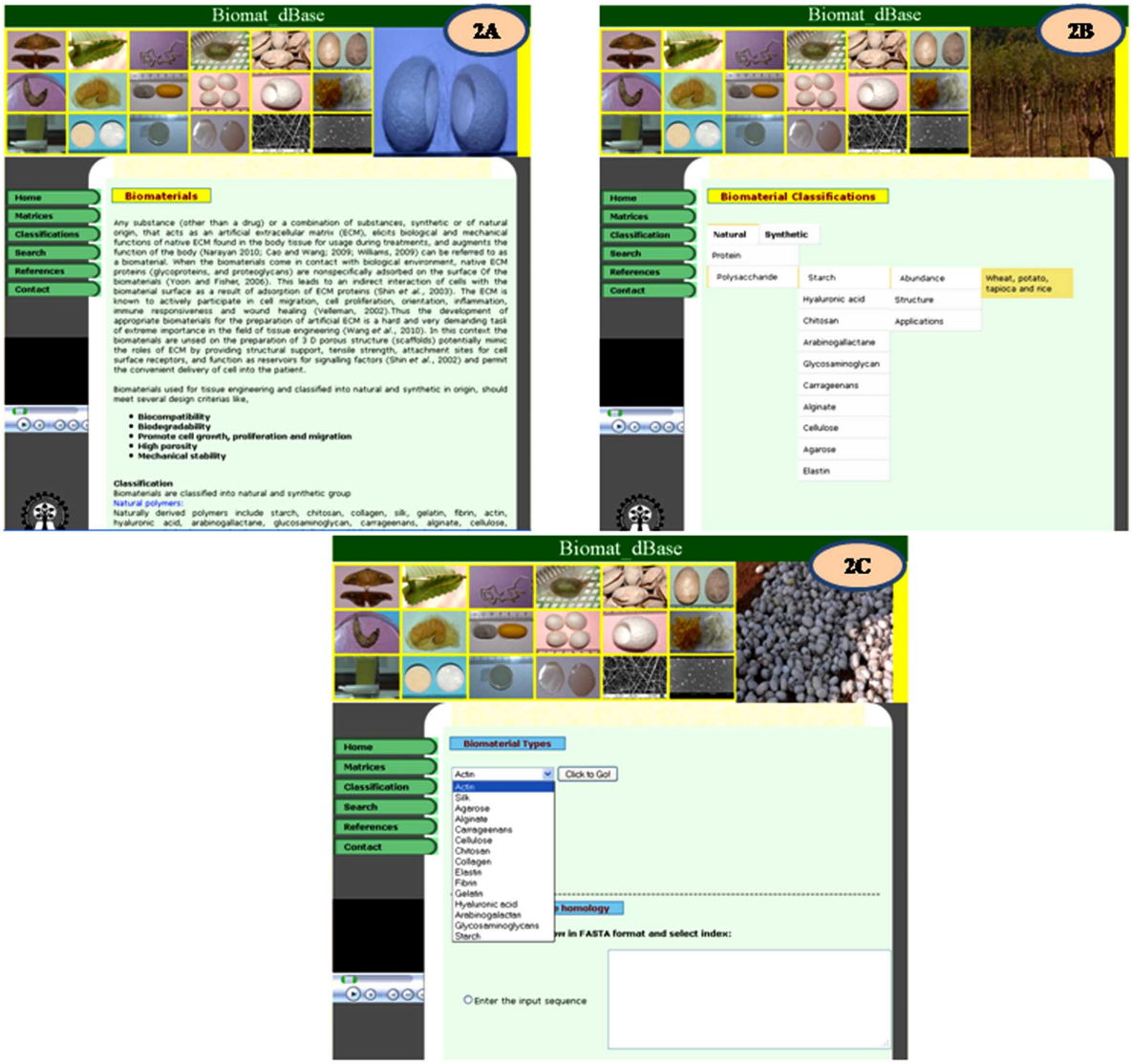

Fig. (2). (**A**). Home page representation of Biomat_dBase (**B**) classification of biomaterials (**C**) a drop down list box represents the structural classifications of biomaterials.

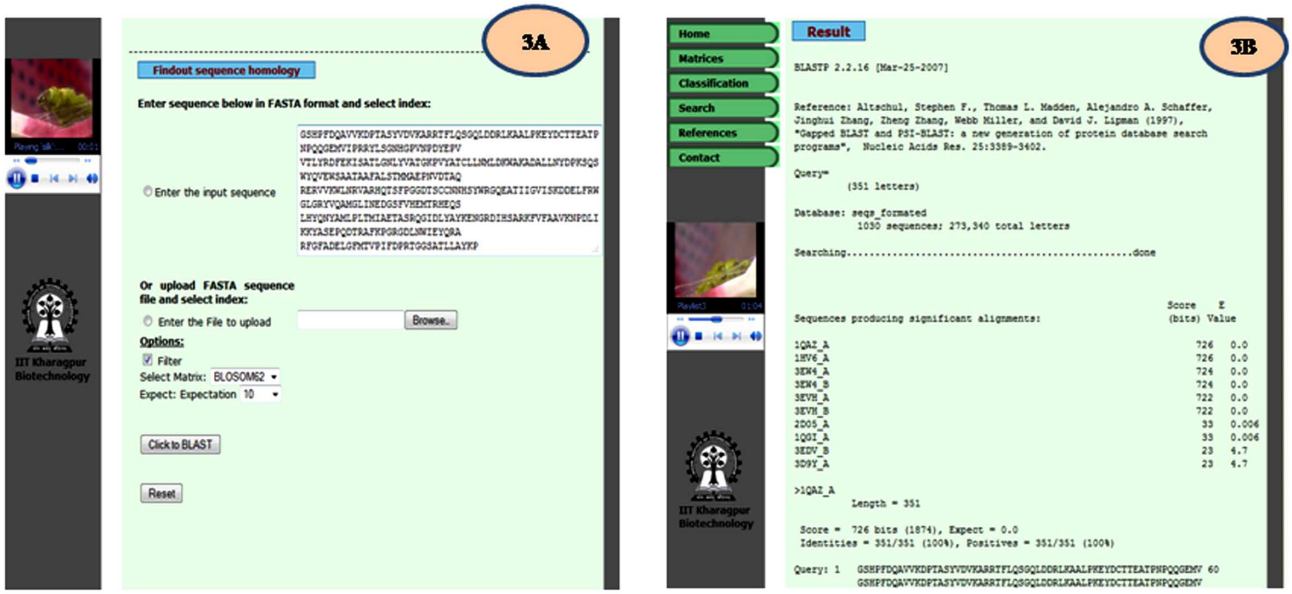

Fig. (3). (**A**). Represents homology search tool based on BLASTp (**B**) depicting the overall representation of BLAST result.

Table 1. Structural Classifications of Starch Biomaterial (as an Example)

PDB ID	Descriptor	Method	Resolution	Keywords	References	Assembly Type	Bound to RNA or DNA	Protein Chains and No. of Residues	Nucleotide Chains and a No. of Residues
1ACO	Glucoamylase, granular starch-binding domain complex with cyclodextrin, NMR, minimized average structure	X-Ray	2.05	Hydrolase	Lauble *et al*. J Mol Biol. (1994) 237:437-51	Monomer	No	A, 754 aa	0
1ACZ	Glucoamylase, granular starch-binding domain complex with cyclodextrin, NMR, 5 structures	NMR		Hydrolase	Sorimachi *et al*. J Mol Biol. (1994) 259 (5):645-661	Monomer	No	A, 108 aa	0
1AMY	Crystal and molecular structure of barley alpha-amylase	X-RAY	2.80	Hydrolase (O-Glycosyl)	Kadziola et *al*., J Mol Biol. (1994) 239:104-121	Monomer	No	A, 403 aa	0
1B90	*Bacillus cereus* BETA-amylase Apo form	X-Ray	2.50	Hydrolase	Mikami *et al*., Biochemistry (1999) 38 (22):7050-61	Monomer	No	A,516 aa	0
1BG9	Barley alpha-amylase with substrate analogue acarbose	X-RAY	2.80	Hydrolase	Kadziola, J Mol Biol. (1998) 278: 205-217	Monomer	No	A, 403 aa	0
1BLI	*Bacillus licheniformis* alpha-amylase	X-RAY	1.90	Hydrolase	Machius *et al.,* Structure (1998)6 (3):281-292	Monomer	No	A, 483 aa	0
1CQY	Starch binding domain of *Bacillus cereus* beta-amylase	X-RAY	1.95	Hydrolase	Yoon *et al*., J. Micro. Biol. (1999) 9:619-623	Monomer	No	A, 99 aa	0
1GAI	Glucoamylase-471 complexed with d-gluco-dihydroacarbose	X-RAY	1.700	Hydrolase	Aleshin *et a*l., Biochemistry (1996) 35 (25): 8319-8328	Monomer	No	A, 472 aa	0
1GCY	High resolution crystal structure of maltotetraose-forming exo-amylase	X-RAY	1.60	Hydrolase	Mezaki *et al*., Biosci Biotechnol Biochem.(2001) 65(1):222-5	Monomer	No	A, 527 aa	0
1HVX	*Bacillus stearothermophilus* alpha-amylase	X-RAY	2.0	Hydrolase	Suvd *et al*., J Biochem. (2001) 129 (3):461-8	Monomer	No	A, 515 aa	0
1G11	Beta-amylase from *Bacillus cereus* var. mycoides in complex with alpha-EPG	X-RAY	2.0	Hydrolase	Hemmi *et al*., J Biochem. (2001) 40:3512-24	Monomer	No	A, 102 aa	0
1KUL	Glucoamylase, granular starch-binding domain, NMR, 5 structures	NMR		Hydrolase	Sorimachi *et al*., J Mol Biol. (1996) 259(5):970-87	Monomer	No	A, 108 aa	0
1OB0	kinetic stabilization of bacillus licheniformis-amylase through introduction of hydrophobic residues at the surface	X-RAY	1.83	Hydrolase	Machius *et al*., J Mol Biol. (1996) 259: 970-987	Monomer	No	A, 483 aa	0
1PEZ	*Bacillus circulans* strain 251 mutant A230V	X-RAY	2.32	Transferase	Leemhuis *et al*., Biochemistry (2003) 42:7518- 26	Monomer	No	A, 686 aa	0
1QHP	Five-domain alpha-amylase from *Bacillus stearothermophilus,* maltose complex	X-RAY	1.70	Hydrolase	Dauter *et al*., Biochemistry (1999) 38:8385 - 8392	Monomer	No	A, 686 aa	0
1RZU	Crystal structure of the glycogen synthase from *A. tumefaciens* in complex with ADP	X-Ray	2.30	Transferase	Buschiazzo *et al*., J EMBO. (2004) 23(16):3196-205	Monomer	No	A, B, 485 aa	0

Table 1. contd…

PDB ID	Descriptor	Method	Resolution	Keywords	References	Assembly Type	Bound to RNA or DNA	Protein Chains and No. of Residues	Nucleotide Chains and a No. of Residues
1TCM	Cyclodextrin glycosyltransferase w616a mutant from *Bacillus circulans* strain 251	X-RAY	2.20	Glyosyl Transferase	Penninga *et al*., J Mol Biol.(1996) 276:32777-84	Monomer	No	A, B, 686 aa	0
1UH4	*Thermoactinomyces vulgaris* R-47 alpha-amylase 1/malto-tridecaose complex	X-RAY	1.80	Hydrolase	Abe *et al*., J.Mol.Biol.(2004) 335:811–822	Monomer	No	A, 637 aa	0
2C3V	Structure of iodinated cbm25 from *Bacillus halodurans* amylase	X-RAY	1.39	Carbohydrate binding module	Boraston *et al*., J Mol Biol. (2006) 281:587	Monomer	No	A, 102 aa B, 102 aa	0
2C4M	Starch phosphorylase: structural studies explain oxyanion-dependent kinetic stability and regulatory control	X-RAY	1.90	Transferase	Purvis *et al*., (2009) (submitted to PDB)	Dimer	No	A, B, C, D 796 aa	0
2DJM	Solution structure of N-terminal starch-binding domain of glucoamylase from *Rhizopus oryzae*	NMR		Sugar binding protein	Liu *et al.,* Biochimica et Biophysica Acta-Gene Regulatory Mechanisms (2007) 403:21-30	Monomer	No	A, 106 aa	0
2FBA	Glucoamylase from *Saccharomycopsis fibuligera* at atomic resolution	X-RAY	1.10	Hydrolase	Sevcik *et al*., FEBS J. (2006) 273: 2161-2171	Monomer	No	A, 492 aa	0
2QZS	Crystal Structure of Wild-type *E.coli* GS in complex with ADP and Glucose(wtGSb)	X-RAY	2.20	Transferase	Sheng *et al*., J Biol Chem. (2009) 284: 17796-17807	Monomer	No	A, 485 aa	0
2VQ4	Carbohydrate-binding of the starch binding domain of *Rhizopus oryzae* glucoamylase in complex with beta-cyclodextrin and maltoheptaose	X-RAY	1.25	Hydrolase	Tung *et al*., J Biochem. (2008) 416(1):27-36	Monomer	No	A, 106 aa	0
2WAN	Pullulanase from *Bacillus acidopullulyticus*	X-RAY	1.65	Hydrolase	Turkenburg *et al*., Proteins (2009) 76(2):516-9	Monomer	No	A, 921 aa	0
2X2H	Crystal structure of the *Gracilariopsis lemaneiformis* alpha-1,4-glucan lyase	X-RAY	1.06	Lyase	Rozeboom *et al.* (2009) (submitted to PDB)	Monomer	No	A,B,C,D 1027 aa	0
2XFR	Crystal structure of barley beta-amylase at atomic resolution	X-RAY	0.97	Hydrolase	Rejzek, M. Mol Biosyst (2011) 7: 718	Monomer	No	A, 535 aa	0
2Y5E	Barley limit dextrinase in complex with beta-cyclodextrin	X-RAY	2.10	Hydrolase	Vester-Christensen *et al*., J Mol Biol. (2010) 403(5):739-50	Monomer	No	A, 858 aa	0
3BC9	Crystal structure of CBM20 domain of human putative glycerophosphodiester phosphodiesterase 5 (KIAA1434)	X-RAY	2.0	Hydrolase	Tan et al., J Mol.Biol (2008) 378: 850-868	Monomer	No	A, 599 aa	0
3BCD	Alpha-amylase B in complex with acarbose	X-RAY	1.35	Hydrolase	Tan et al., J Mol.Biol (2008) 378: 850-868	Monomer	No	A,599 aa	0

Table 1. contd…

PDB ID	Descriptor	Method	Resolution	Keywords	References	Assembly Type	Bound to RNA or DNA	Protein Chains and No. of Residues	Nucleotide Chains and a No. of Residues
3CK7	Structure of cyclodextrin glycosyltransferase complexed with its main product beta-cyclodextrin	X-RAY	2.40	Glycosyltransferase	Schmidt *et al.,* Biochemistry (1998)37 (17):5909-15	Monomer	No	A,B,C,D 527 aa	0
3COP	*B. thetaiotaomicron* SusD	X-RAY	1.50	Sugar binding protein	Koropatkin *et al*., Structure (2008)16(7):1105-15	Monomer	No	A, 485 aa	0
3D1J	Crystal Structure of *E.coli* GS mutant E377A in complex with ADP and oligosaccharides	X-RAY	2.29	Transferase	Sheng *et al*., J Biol Chem. (2009) 284: 17796-17807	Monomer	No	A,477 aa	0
3K8L	Crystal structure of SusG	X-RAY	2.20	Membrane Protein	Koropatkin *et al.,* Structure(2008)l (7):1105-15	Monomer	No	A,B, 669 aa	0
3NCH	Glucose-6-Phosphate activated form of Yeast Glycogen Synthase	X-RAY	2.41	Transferase	Baskaran *et al*., Proc Natl Acad Sci. (2010) 107: 17563-17568	Tetramer	No	A,B,C,D, 725 aa	0
3O3C	Structure of a plant phosphatase	X-RAY	2.40	Hydrolase	Baskaran *et al*., Proc Natl Acad Sci. (2010) 107: 17563-17568	Tetramer	No	A,B,C,D, 725 aa	0
3O7Z	Crystal Structure of *E.coli* Branching Enzyme in complex with linear oligosaccharides	X-RAY	2.41	Transferase	Feng *et al.,* Biochemistry (2011) 50 (14) :2919-30	Tetramer	No	A,B,C,D, 612 aa	0
5BCA	Deletion mutant delta (145-150), f151d of cyclodextrin glycosyltransferase	X-RAY	2.60	Glyosyltransferase	Oyama *et al*., J Biochem. (1999) 125: 1120-1130	Monomer	No	A,B,C,D, 516 aa	0
5CGT	Beta-amylase from *Bacillus cereus* var. mycoides	X-RAY	2.20	Hydrolase	Parsiegla *et al.,* Eur.J.Biochem (1998) 255: 710-717	Monomer	No	A,684 aa	0

in FASTA formats, structure descriptions, methods of structural salvations and resolutions, keywords of the related proteins, assembly type of the proteins whether the proteins are bound to RNA or DNA, protein chains and number of residues, nucleotides and number of residues, and their related references as shown in the Fig. (**2C**). All the entries are displayed in a tabular format on the webpage. An example on starch biomaterial is shown in Table **1**.

The entry page of BLAST explore is a simple programme that receives only a single FASTA formatted query sequence as an input. This allows the selection of the BLASTP alignment algorithm. This will take the database sequences from the PDB, the selection of BLAST e-Value threshold, the option of filtering low complexity sequence segments and BLAST Matrix. Fig. (**3A**) represents the BLASTp homology search page. The BALST result page shows the bit score, e-value, sequence alignment and homology sequence with the biomaterial database. The BLAST output thus generated is represented in the form of a web shot as shown in Fig. (**3B**). Further, an input parameter, called threshold, should be defined by the users to start the search. The server takes the query from the input page, searches for similar protein and polysaccharide sequences against the biomaterial database using the BLASTP program. Finally, similar sequences which are obtained under the given threshold value are displayed in a new window.

We have put reference modules for the related biomaterials; interested users may also browse through it to retrieve the useful information from the literature. This will help researchers in designing their experiments.

CONCLUSIONS

A major feature of this biomaterial database is the ability to browse through the content. Most of the data are displayed in the form of RDBMS that are integrated in a hierarchical manner. This enables the browsers to display the required data by moving the mouse over it. Based on this, the database is designed for providing a platform for information on biomaterials. For avoiding the unnecessary duplication of research and for efficient utilization of resources and sharing of contents biomaterial database is necessary. This database is focused on the biomaterial types and their characteristics (occurrence, structure and applications). The search tool option provides information related to homology query sequences against all fifteen types of protein and polysaccharides biomaterials based on BLAST search tool.

For a particular protein or polysaccharide, RDBMS is designed to classify the data on the basis of their structures. BLAST explore provides a simple initiative and interactive graphical representation of the BLAST results. We have projected by pictorial diagram on the fabrication of different biomaterial matrices from silk protein biomaterials for different biomedical and tissue engineering applications as an example. This will be helpful for the researchers to get the initial idea how to proceed with the fabrication of biomaterial matrices. This database will help biologists and material scientists to build their own database for sequence similarity and for predicting homology of related query sequences. The users can retrieve the useful information related to natural and synthetic biomaterials from this database. We display some pictures of biomaterials obtained from silk proteins at web page as an example. The silk protein as a biomaterial mimics the natural material extremely well [67]. Biomaterial database is easily accessible and created by the optimization of data and development of common minimum standard for sharing such resources. Inspite of many efforts, still there is no standard protocol for developing a biomaterial database that caters to a specialized area. A continuous critical assessment in this field and dialogue among the academicians and programmers will contribute immensely in knowledge sharing and scientific advancement. The authors recognize this is a first step towards the organization of data integration. We also look forward to increasing network effect benefits for the entire biomaterials community as adoption accelerates and improves to the standard are implemented.

SUPPLEMENTARY DATA

Biomaterial database is freely available on the site http://dbbiomat.iitkgp.ernet.in. Questions, comments and suggestions from the users are welcome for future up gradation.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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